Interview Summary

Applicants thank Examiner Hutson for the telephonic Interview held April 24, 2007. During that interview the rejections of record were discussed, as was a proposed amendment of claim 8 to address the rejection under 35 U.S.C. § 102(b).

Claim Status

Upon entry of the foregoing amendments, claims 8-13, 56, and 70-75 are pending in the application, with claim 8 being the independent claim. Claims 1-7, 14-55, and 57-69 have been cancelled. Claim 8 is currently amended. Support for the amendments to claim 8 can be found throughout the Specification. See, for example, at page 26, first paragraph (Example 1). Thus, no new matter is added by way of these amendments, and their entry is respectfully requested.

Remarks

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider and withdraw the outstanding rejections.

Rejection Under 35 U.S.C. § 102(b)

Claims 8-12, 56 and 70-73 were rejected under 35 U.S.C. § 102(b) as being anticipated by Major *et al.*, *Biotechniques 12*:40-43 (1992), ("Major") as evidenced by Deana and Belasco, *Mol. Microbiol. 51*:1205-1217 (2004). Applicants respectfully traverse this rejection.

An anticipation rejection under 35 U.S.C. § 102 requires a showing that each limitation of a claim is found in a single reference, practice or device. See Kalman v. Kimberly Clark Corp., 713

F.2d 760, 771 (Fed. Cir. 1983), cert. denied, 465 U.S. 1026 (1984). See also M.P.E.P. 8th ed., § 2131 (rev. 2, May 2004) ("To anticipate a claim, the reference must teach every element of the claim.").

The present claims are drawn to a method for synthesizing a nucleic acid molecule from a preparation containing RNA and double-stranded DNA. The claimed method comprises:

a) *adding to the preparation one or more exogenous DNA polymerases, and one or more exogenous peptides or polypeptides having ribonuclease activity*, wherein the peptides or polypeptides having ribonuclease activity are capable of degrading single-stranded RNA; and

b) incubating the mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of the double-stranded DNA and under which the peptides or polypeptides having ribonuclease activity degrade the single-stranded RNA.

The Major reference does not teach a method that includes all of the steps encompassed by the currently presented claims. In particular, Major does not disclose the step of adding one or more exogenous DNA polymerases and one or more exogenous peptides or polypeptides having ribonuclease activity to a nucleic acid preparation. Rather, Major discloses adding a DNA polymerase, but not an exogenous peptide or polypeptide having ribonuclease activity, to a nucleic acid preparation. For at least this reason, Applicants request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 8-12, 56, 70, 71, and 73 are rejected under 35 U.S.C. § 103(a), as being unpatentable over Major *et al.*, *Biotechniques 12*:40-43 (1992), ("Major"), and Maudru *et al., J. Virological Methods 66*:247-261 (1997), ("Maudru"). Applicants respectfully disagree.

Legal Standard

To establish *prima facie* obviousness the Examiner must provide a convincing line of reasoning showing the desirability of combining references in such a manner as to arrive at the claimed invention. *See* In re Deminski, 796 F.2d 436, 230 USPQ 313 (Fed.Cir.1986), In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) and MPEP 2142. The Examiner's reasoning must not use the application "as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims. Monday morning quarterbacking is quite improper when resolving the question of nonobviousness." *See* Orthopedic Equipment Co. v. United States, 702 F.2d 1005, 1012, 217 U.S.P.Q. 193, 202 (Fed. Cir. 1983). Rather, "measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. *See*, e.g., In re Dembiczak v. Zinbarg,175 F.3d 994 (Fed. Cir. 1999) and In re W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 UPSQ 303, 313 (Fed.Cir.1983).

Thus, knowledge of the Applicant's disclosure must be put aside in reaching the determination of obviousness, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. *See* MPEP 2142. Then, in

view of all factual information, the examiner must make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. In particular, where the claimed invention solves a problem, the discovery of the source of the problem and its solution are considered to be part of the "invention as a whole." *See* In re Kaslow, supra; In re Nomiya, 509 F.2d 566, 184 USPQ 607 (CCPA 1975); and In re Sponnoble, 405 F.2d 578, 160 USPQ 237 (CCPA 1979).

The Examiner must not only consider the invention as a whole, but must also consider the prior art in its entirety, including those parts that teach away from the claimed invention. *See* W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). The Supreme Court recently indicated that teaching away from a claimed invention is a likely indicator that the invention is not obvious: "[W]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *See* KSR Intern. Co. v. Teleflex Inc., 127 S.Ct. 1727, 1740 (2007). Thus, an "applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." *See* In re Geisler, 116 F.3d 1465, 1469 (Fed. Cir. 1997). The Federal circuit has also stated that "a reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by applicant." *See* In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

Summary of Claimed Subject Matter

The present claims 8-12, 56, 70, 71, and 73 are drawn to methods for synthesizing nucleic acid molecules from a preparation containing RNA and double-stranded DNA. The claimed methods involve:

a) adding to the preparation one or more exogenous DNA polymerases, and one or more exogenous peptides or polypeptides having ribonuclease activity, wherein the peptides or polypeptides having ribonuclease activity are capable of degrading single-stranded RNA; and

b) incubating the mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of the double-stranded DNA and under which the peptides or polypeptides having ribonuclease activity degrade the single-stranded RNA.

The Cited Art

Major teaches a rapid PCR assay for screening point mutations. *See* Major at abstract. The basic principle behind Major's assay is that PCR amplification should yield products only when the 3'-terminal nucleotide of a primer is matched with a DNA template, and should not yield products when the 3'-terminal nucleotide of a primer and template are mismatched. *See* Major at page 42, left column. Counter to his original expectation, however, Major observed some amplification products (*i.e.*, "extra minor bands") when using T:T mismatched primers and bacterial colony lysates as the starting material for template DNA. *Id.*

Maudru teaches a modified, highly sensitive PCR-based reverse transcriptase (PBRT) assay. *See* Maudru at abstract. Specifically, Maudru teaches that background signal of his PBRT-type assay can be eliminated by inserting an RNase digestion step between the step of reverse transcription of an RNA template and the subsequent step of PCR amplification. *Id.* Maudru goes

on to surmise that the observed background signal of the PBRT assay might be due to an intrinsic RNA-dependent DNA polymerase activity of *Taq* DNA polymerase. *Id.* and at page 248, last paragraph.

Remarks

The Examiner has not presented a convincing line of reasoning showing the desirability of combining the cited references in such a manner as to arrive at the claimed invention. The Examiner has argued that (1) Maudru teaches reverse transcription (RT) of commercially available RNA templates followed by RNase treatment of the resulting single-stranded cDNAs to eliminate background from subsequent PCR reactions, and (2) that skilled artisans therefore would have been motivated to add a preliminary RNase digestion step in PCR of double-stranded DNA from bacterial lysates as disclosed by Major. The Examiner's argument falls short of establishing *prima facie* obviousness for at least the following reasons.

First, while skilled artisans at the time the present application was filed understood that cell lysates such as those used in Major's PCR assay contained many factors (including, for example, RNA as well as a variety of cellular proteins, salts, lipids, signaling molecules, metabolites, *etc.*), they did not appreciate which of those factors might be responsible for the unexpected products (*i.e.*, the "extra minor bands") observed in PCR reactions using such lysates. For example, Major himself identified various factors he thought might influence PCR of double-stranded DNA from complex samples like cell lysates in assays using mismatched primers, and RNA was not among the factors he identified. Similar conclusions were true for other investigators who employed PCR assays like Major's. *See*, for example, Kwok *et al.*, *Nucl. Acids Res.* 18:999-1004 (1990), Wu *et al.*, *Proc. Natl. Acad. Sci. USA* l86:2757-2760 (1989) and Charlieu, "Chapter 12, Distinction Between Almost-

Identical DNA Sequences by Polymerase Chain Reaction," in PCR Technology Current Innovations, pp. 101-106, Griffin and Griffin Eds., (1994) as described in Applicants' Appeal Brief filed October 24, 2006 at page 15. The inescapable fact is that skilled artisans did not recognize at the time the present application was filed that RNA could be a problem for PCR of double-stranded DNA in complex samples, like cell lysates, much less that adding RNase activity to such PCR reactions would provide any benefit whatsoever. This could be because, as the Action states on page 3, a lysate mixture "inherently comprises ribonucleases" and skilled artisans at the time just did not consider the effect of adding more. In fact, it was only the Applicants who actually understood and appreciated that adding RNase to such complex DNA preparations could solve the problem of contaminating RNA. Whatever the reason, skilled artisans simply did not recognize the problem that RNA could pose for PCR of double-stranded DNA in complex samples like a cell lysate, and consequently could not, and did not, contemplate including RNase to degrade the contaminating RNA, as is presently claimed. This discovery of the source of the problem and its solution are part of the "invention as a whole," and must be recognized by the Examiner. *See* In re Kaslow, supra; In re Nomiya, 509 F.2d 566, 184 USPQ 607 (CCPA 1975); and In re Sponnoble, 405 F.2d 578, 160 USPQ 237 (CCPA 1979).

Second, the Major reference actually teaches away from the claimed invention. Like other skilled artisans at the time (including, for example, Charlieu, Wu *et al.*, and Kwok *et al.*), Major did not understand the problem that contaminating RNA presented and attributed that problem to something else entirely (*i.e.*, "spurious PCR amplification" of template DNA). Instead, what Major focused on was a different perceived problem, namely poor primer discrimination, which he rectified through the use of Perfect Match PCR Enhancer™ (which is thought to destabilize

mismatched primer-template complexes)." *See* Major at page 42, middle column and Stratagene Instruction Manual for Perfect Match™ PCR Enhancer (Catalog #600129). Thus, the Major reference, considered in its "entirety," would have lead skilled artisans in a direction divergent from the path that was taken by the Applicants – in a way that would not have lead a skilled artisan to combine the cited references in such a manner as to arrive at the claimed invention. As is the case here, "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *See* KSR Intern. Co. v. Teleflex Inc., 127 S.Ct. 1727, 1740 (2007).

For at least the reasons discussed above (*e.g.*, those skilled in the art did not appreciate the problem solved by the claimed invention, and because Major teaches away from the claimed invention), skilled in the art would not have been inclined to combine the cited references. Thus, *prima facie* obviousness has not been established and Applicants therefore request that the rejection of claims 8-12, 56, 70, 71, and 73 under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all presently outstanding rejections. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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